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**Health Policy Advisory Committee on
Technology**

Status report

Brain implant to predict epileptic seizures

November 2013

HealthPACT
emerging health technology



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This status report was prepared by Linda Mundy from the HealthPACT Secretariat.

Technology, Company and Licensing

Register ID	WP185
Technology name	Brain implant device to predict epileptic seizures
Patient indication	For patients with uncontrolled, drug-resistant epilepsy

Description of the technology

This is a brief Status Report summarising the initial results of the first study in humans by Cook et al (2013)¹, which described the use of an implanted device to predict seizures in patients with severe, uncontrolled epilepsy.

The seizure advisory system is a small, hand-held device that receives and analyses electroencephalography (EEG) signals. The device, as described in Figure 1, consists of an array of intracranial electrodes placed on the surface of the cortex that collect EEG data from the hemisphere that generated the most frequent stereotypical seizures. Data is transmitted via implanted leads connected to a subclavicular implanted telemetry unit. Each patient had a unique algorithm developed for their system, which required the collection of EEG data (including at least 5 leading seizures) for at least one month post-operatively. The implanted unit wirelessly transmits data to the hand-held device, which then applies the unique algorithm to the data, resulting in an advisory signal: blue, white and red signals representing a low, moderate or high likelihood of seizure, respectively. It is hoped that these signals give patients adequate time to prepare themselves for a seizure, to take aversive action in order to avoid potentially dangerous scenarios and to allow acute drug delivery rather than chronic drug administration.

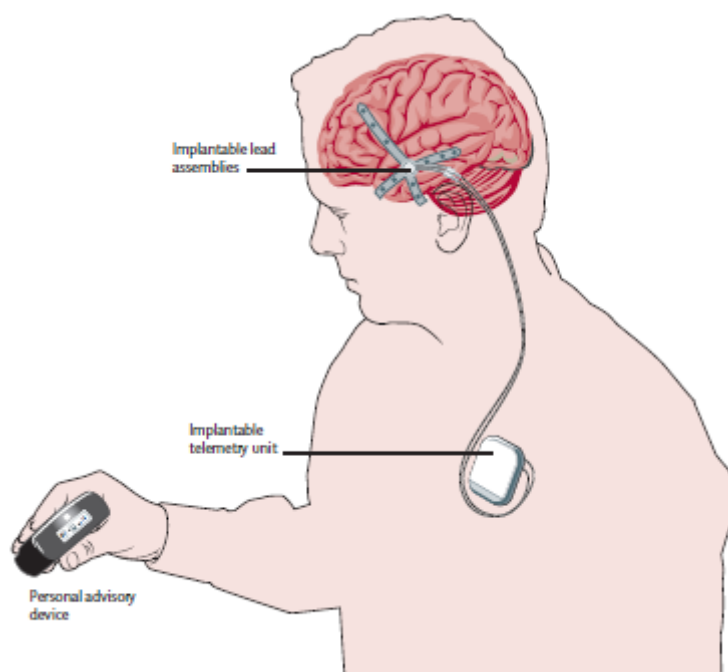


Figure 1 The seizure advisory system consisting of intracranial leads ¹

Reason for assessment

This status report was prepared to alert policy makers to the potential of this technology – in that the device has the potential to improve the quality of life in patients who have few therapeutic options. Although this device does not provide a therapeutic solution to uncontrolled or refractory epilepsy, it does lend a degree of planning to the patient who, in the knowledge that a seizure is imminent, could avoid potentially dangerous activities and adjust their medication accordingly.

Stage of development in Australia

- | | |
|--|---|
| ☐ Yet to emerge | ☐ Established |
| ☒ Experimental | ☐ Established <i>but</i> changed indication or modification of technique |
| ☐ Investigational | ☐ Should be taken out of use |
| ☐ Nearly established | |

Licensing, reimbursement and other approval

This device is still in the experimental research phase and as such is not approved by any licensing body.

Australian Therapeutic Goods Administration approval

- | | |
|---|-----------------|
| ☐ Yes | ARTG number (s) |
| ☒ No | |
| ☐ Not applicable | |

Technology type

Diagnostic

Technology use

Diagnostic

Patient Indication and Setting

Disease description and associated mortality and morbidity

Epileptic seizures are a neurological disorder in which the brain's normal electrical activity is temporarily disrupted by excessive hypersynchronous neuronal activity; however seizures are not synonymous with epilepsy. Epilepsy is defined as a chronic tendency to have recurrent, unprovoked seizures. Epileptic seizures can be categorised as either focal or generalised seizures. Focal seizures, which originate within neuronal networks limited to one cerebral hemisphere, produce signs and symptoms corresponding to the specific region of the brain that is affected by the seizure. Focal seizures may affect motor function, sensory function (auditory, olfactory and visual) or may be dyscognitive, with alterations in consciousness or awareness. Generalised seizures rapidly affect both cerebral hemispheres, and their clinical expression is consistent with substantial involvement of both sides of the

brain. This may take the form of convulsive seizures (or grand mal seizures), which result in the patient becoming stiff, usually with limb and body extension. Breathing halts, and cyanosis and urinary incontinence is common. Spontaneous respiration usually resumes within one minute. After 15 to 45 seconds, the tonic activity gives way to clonic seizures that are rhythmic, and may be associated with asymmetrical jerking of all four limbs. Post-seizure stupor may persist, and patients will generally sleep for 2-8 hours, experience headaches, sore muscles and an inability to concentrate. Some patients may experience memory loss after a tonic-clonic seizure. Absence seizures (or petit mal seizures) are characterised by an abrupt onset and termination of a momentary lapse of awareness. These seizures can occur many times a day but are not associated with progressive neurologic disease. Myoclonic seizures consist of brief episodes of sudden motor contraction, with one arm involved, or bilateral and massive, with involvement of both upper extremities and the trunk. Consciousness is maintained but these seizures may be difficult to evaluate due to their short nature.²

The 2010 Australian Epilepsy Longitudinal Survey collected data from the 621 participants from the Australian Epilepsy Research Register. A total of 343 participants responded (55% response rate), and of these 188 (55%) reported suffering an injury as a result of a seizure. A majority of these injuries resulted in hospitalisation (121/188, 64%). Many of the survey respondents experienced more than one type of injury. Of a total of 272 reported injuries, the most common were soft tissue injuries (159/272, 58%), followed by fractures (49/272, 18%), burns (17/272, 6.3%) and concussion (17/272, 6.3%). Although other injuries were small in number, they were of a more serious nature: dislocation (n=8), fall (n=8), near drowning (n=4), acquired brain injury (n=4), motor vehicle accident (n=4), aspiration (n=2) and whiplash (n=1). In addition, nine per cent of all respondents reported dental injuries as a result of a seizure.³

In 2008, the Australian Bureau of Statistics reported epilepsy (ICD-10 code G40) as the underlying cause of death in 259 people, corresponding to an age standardised death rate of 1.2 per 100,000, equating to 6,845 years of potential life lost.⁴

Number of patients

There is little recent data on the prevalence of epilepsy in Australia. It is estimated that epilepsy (defined as recurrent—two or more—unprovoked seizures) affects more than 62,000 Australians, with a prevalence of 340 per 100,000 in 1996. The data suggest that epilepsy has an incidence of 30 per 100,000 per year in Australia.⁵ In the 2001 National Health Survey, 120,300 Australians self-reported that they had epilepsy.⁶

In 2009-10, there were 15,826 public hospital separations for epilepsy with an average length of stay of three days. However, it should be remembered that this figure does not represent the number of patients as an individual may have multiple hospital separations.⁷

Speciality	Neurology and neurosurgery
Technology setting	Specialist hospital

Impact

Alternative and/or complementary technology

Substitution technology: New technology is a direct substitute for current technology, or will substitute to a great extent.

Current technology

There is currently no technology available that can predict imminent seizures. Until recently, all studies about seizure prediction were based on the retrospective assessment of EEGs.⁸

The mainstay of epilepsy treatment is the use of anti-epilepsy drugs (AEDs), which aim to inhibit the abnormal discharge of neurons. The choice of medication depends on the type of seizure, with some AEDs effective for specific types of seizures, whereas other AEDs can worsen other types of seizures, and tolerability. For example ethosuximide and valproic acid are effective in childhood generalised epilepsy, ethosuximide having utility only in this setting, whereas gabapentin and levetiracetam are often more appropriate for elderly patients as they are less sedating with fewer drug interactions. Among patients presenting with a new diagnosis of epilepsy, approximately 65 per cent achieve seizure remission on AED treatment, either mono- or poly-therapy. However, approximately one third of patients are considered to be *drug resistant*. In these patients, other forms of treatment, including surgery, should be considered. In addition, intolerable side effects from AEDs are a major cause of poor compliance with treatment.²

There are a number of surgical interventions used to treat refractory epilepsy including vagus nerve stimulation (application number 1358, deemed a suitable MSAC application in July 2013), temporal lobe resection, usually performed in adults, and cortical resective surgery, which aims to remove the portion of the brain from which the epileptic activity originates.² Temporal lobe resection has been observed as the most successful surgical treatment effect is seen for compared with medical therapy. Seizure freedom is achieved in 70 per cent of patients after temporal lobe resective surgery, and 95 per cent of patients achieve a 90 per cent reduction in symptoms.⁹ Promising surgical therapies for epilepsy include radiosurgery and various types of electrical stimulation of the brain. Palliative surgical procedures, such as callosotomy and multiple subpial transections, have lower success rates compared to conventional surgical procedures and are used when surgical resection of the seizure focus is not possible.²

Diffusion of technology in Australia

This research is currently being conducted at St Vincent's and the Royal Melbourne Hospitals (Melbourne), Departments of Medicine and Surgery, University of Melbourne, Austin Health (Victoria) and NeuroVista Corporation (Seattle, USA).¹

Cost infrastructure and economic consequences

Use of a predictive device may mean many patients could move away from the long-term use of AEDs to on-demand therapy to prevent seizures from occurring including anticonvulsants or electrical stimulation, which may present a possible cost-saving.⁸ No pricing information could be ascertained as the device is in the development stage.

Evidence and Policy

Safety and effectiveness

The proof-of-concept study published by Cook et al (2013) is the first study to use EEG data to prospectively predict the onset of seizures.¹

Fifteen adult patients (average age 44.5 ± 13.0 years, range 20-62 years) from three Melbourne hospitals participated in the study. All patients with the exception of one were taking at least one AED, with 11 patients taking three or more AEDs. Six patients had undergone previous resective surgery, and one of these patients had also undergone vagus nerve stimulation. Baseline seizure rates were collected for 3-months prior to implantation and all patients experienced between two and 12 seizures per month. After implantation with the device, intracranial EEG data were collected for at least 1-month without advisory signals being given until sufficient data was available to create a unique patient algorithm. Once the algorithm was created, patients moved into the advisory stage, with visible and auditory signals indicating a seizure.

At 4-months post-implantation there were a total of 11 device-related adverse events, two of which were considered serious, requiring intervention (Table 1Table 1). In one patient the sutures fastening the device failed, possibly due to a fall experienced during a seizure. This resulted in the device migrating, causing discomfort and required a further procedure to fasten the unit. Another patient experienced persistent headaches and imaging revealed fluid accumulation on the dura around the surgical wound, which required a second procedure to drain. Both patients recovered fully.

At 12-month follow-up, two further serious adverse events were reported. One patient presented with an infection near the implanted device at 7-months. During evacuation of the infection site, the leads of the device were found to be damaged, resulting in the need to fully explant the device. The same patient who experienced device migration at 4-months reported neck discomfort caused by the tautness of the leads, and device explanation was requested. A further cosmetic procedure was required in this patient. In addition, many

patients reported difficulties with the cosmetic appearance of the device, in that the telemetry unit was prominent, however this was considered a minor problem.

Table 1 Adverse events at 4- and 12-months post-implantation

	Adverse events		Serious adverse events	
	4-months	12-months	4-months	12-months
Device migration	1		1	
Device-related infection		1		1
Reaction at site of device	1	1		1
Post-operative nausea	1			
Post-operative vomiting	1			
Procedural headache	5			
Procedural pain	1			
Seroma	1		1	

Compared to baseline, no patients demonstrated any significant neuropsychological changes at follow-up. One patient withdrew from the study early due to tethering of the leads. All of the remaining 14 patients accrued sufficient data to construct an algorithm, however only 11 of these had an algorithm that met the enabling criteria and progressed to the advisory phase of the study. Patient four was withdrawn prior to 4-month follow-up due to explanation of the device.

Patients were also asked to record any seizure events in a diary. Interestingly, self-reported seizures considerably under-estimated the actual number of seizures as captured by intracranial EEG. This finding may have implications for trials of new epilepsy treatments which may use self-reported data as a primary endpoint, as well as for routine management. All seizures of two patients occurred during the red advisory phase, indicating that the device had 100 per cent sensitivity for these two patients (patients 2 and 14, Table 2). Of concern is the time patients spent in the red advisory phase (high likelihood of seizure) without a seizure occurring, which may result in psychological harms to the patient. At four months the mean warning time of the red advisory was 114 minutes $\pm$ 151 minutes (range 5-960 minutes). The blue advisory signal (low likelihood of seizure) had a negative predictive value of 98–100 per cent in the five patients in which it was enabled, indicating that the lack of a warning signal provides the patient with the reassurance that a seizure is not likely. At the end of the initial 4-month advisory period, there was no significant improvement or decline in clinical effectiveness measures compared to baseline. Some patients had difficulty interpreting and applying the predictive data to gain a clinical benefit, especially those patients who experienced long periods when the device was in the red advisory. Those

patients who spent the least amount of time in the red advisory reported the greatest satisfaction with the device as they were able to put in place behaviour modifications and to warn bystanders that a seizure was imminent in the short-term.

Table 2 Algorithm performance by patient during the first 4-months of the advisory stage

	Time spent in advisory (%)		Seizures (n)*	High-likelihood performance		
	High	Low		Sensitivity	p value	Likelihood ratio
Patient 1	27	7	7 (13)	86% (77%)	0.0017 (0.0002)	14.3 (8.0)
Patient 2	31	56	3	100%	0.0266	All**
Patient 3	29	1	58 (106)	56% (45%)	<0.0001 (0.0001)	3.1 (2.1)
Patient 8	28	Not enabled	36 (86)	63% (62%)	0.0003 (<0.0001)	4.4 (4.2)
Patient 9	11	48	49 (52)	18% (17%)	0.0839 (0.1419)	0.8
Patient 10	17	Not enabled	109 (164)	54% (51%)	<0.0001	5.8 (5.1)
Patient 11	15	26	11 (39)	56% (39%)	0.0039 (0.0003)	5.1 (2.6)
Patient 13	28	Not enabled	26 (113)	57% (50%)	0.0021 (<0.0001)	3.4 (5.1)
Patient 14	3	88	3	100%	<0.0001	All**
Patient 15	41	Not enabled	21 (24)	71%	0.0034 (0.0019)	3.6 (3.5)

* Seizures: assessments based on the use of clinical equivalent seizures in addition to correlated clinical seizures are in brackets, when different

** All events occurred during the high-likelihood advisory

The likelihood ratio = ([the number of events in high advisory]/[time in high advisory])/([number of events in moderate advisory]/[time in moderate advisory])

Subsequent to the 4-month end-point reported, further refinements of the algorithm took place to improve the prediction statistics. It is hoped that with future iterations of the device, the greater number of events recorded from individuals will improve the algorithm, enabling even more reliable seizure forecasting (personal communication from the authors).

Other prediction/detection/treatment systems are currently under development. The European Commission is supporting Epilepsiae^a – the Epilepsy Project, which is bringing together research from a number of European centres to develop Brainatics, a transportable alarming device, which will automatically record data, predict and warn the patient of

^a Epilepsiae - Evolving Platform for Improving the Living Expectations of Patients Suffering from Ictal Events

epileptic seizures. The project is evaluating seizure prediction algorithms using software called EPILAB and this will be made publicly available once the project has finished.¹⁰

In November 2013, the NeuroPace® RNS® System (NeuroPace Inc, USA) received premarket FDA approval. The RNS System is not a prediction device per se, but a neuro-stimulator implanted in the cranium for the treatment of refractory epilepsy. The system is designed to detect abnormal electrical activity in the brain and respond by delivering an imperceptible level of electrical stimulation to normalise brain activity *before* an individual experiences a focal seizure (also referred to as partial onset seizures).¹¹ Once implanted the treating clinician adjusts the detection and stimulation parameters for each patient to optimise control of their seizures.¹² NeuroPace intends to market their system in Australia and New Zealand but are uncertain of their marketing timeline. The system has multiple components, and depending on the components selected the purchase cost of the full system is likely to be approximately US\$40,000 (personal communication NeuroPace).

The pivotal NeuroPace® RNS® System FDA approval trial was a US multi-centre randomised controlled trial (level II intervention evidence).¹² Although 240 patients were enrolled, only 191 patients (mean age 34.9 ± 11.6 years, range 18-66 years) met the inclusion criteria of having an average of ≥ 3 disabling partial onset seizures per month that were not controlled with the use of ≥ 2 AEDs. Subjects were randomised 1:1 to the active stimulation (n=97) or sham stimulation (n=94) treatment group.

Baseline seizure data was collected on all patients for 12-weeks prior to implantation. In addition, all patients underwent a 4-week post-implantation period at the end of which time randomisation took place. All patients underwent implantation with the device, however the device was not activated in the sham group during the 4-week optimisation and 12-week and assessment periods. Management of the neuro-stimulator was not blinded, however collection of outcome data was blinded. After the 12-week blinded evaluation period, all patients were able to receive active responsive stimulation over 84-weeks, with 12-month follow-up data available for all patients (Figure 2).

There were no differences between the baseline characteristics of the two treatment arms, including age, sex, the number of years with epilepsy (mean 20.5 ± 11.6 years, range 2-57 years), number of daily seizures (mean 1.2 ± 2.2) or the number of patients with two seizure foci. Overall, 32 per cent of patients had undergone previous therapeutic surgery and 34 per cent had undergone vagus nerve stimulation.¹²

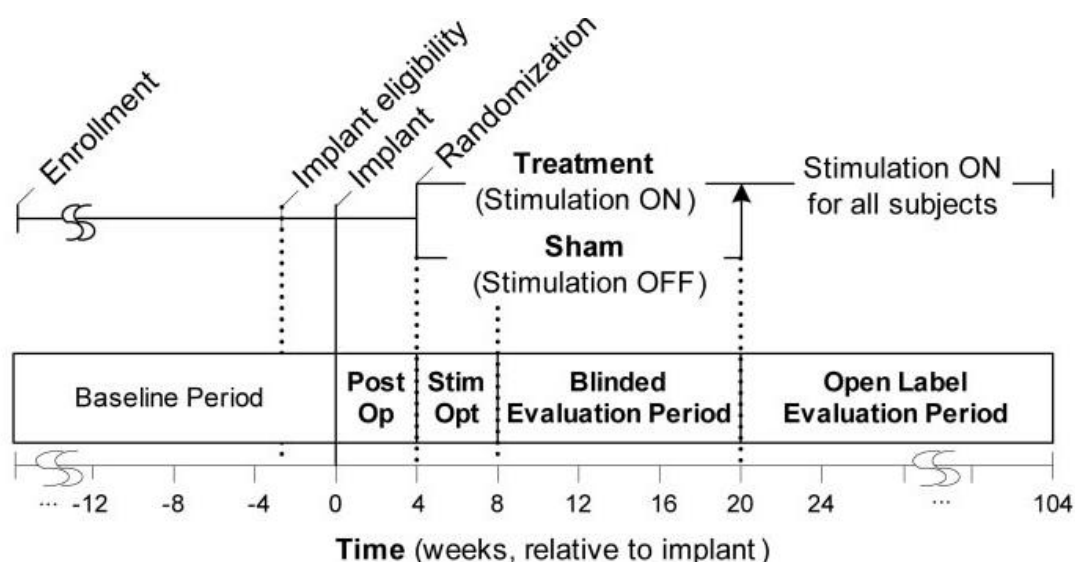


Figure 2 Timeline describing enrolment, randomisation, evaluation period (treatment vs sham) and open label period (all patients with active stimulation) ¹²

Adverse events were reported as either serious or mild, and as device-related or not-device related. Overall, the rate of serious adverse events was 12 and 18.3 per cent during the 4-week post-operative period and the 12-week evaluation period, respectively. There was no difference in the number of serious or mild adverse events between the two groups during the evaluation period. A total of six patients died during the study period: one from lymphoma, one with a history of depression committed suicide and four were attributed to sudden unexplained death in epilepsy, three of whom were in the active stimulation group. Intracranial haemorrhage occurred in nine patients (4.7%), with six occurring in the post-operative period. The remaining three were subdural haematomas attributed to seizure-related head trauma. These patients did not experience any permanent neurologic sequelae. Ten patients (5.2%) experienced an implant or incision site infection, which resulted in the removal of the device in four patients. Although many patients entered the trial with a history of verbal memory dysfunction, visuospatial memory dysfunction and depression, there was no deterioration in any neuropsychological measures at the end of the evaluation period or at end of follow-up. ¹²

Overall, the mean seizure frequency was significantly reduced in the treatment group compared to the sham group ($p=0.012$) (Table 3). At the end of the first month of the evaluation period, both the treatment and sham groups reported a decrease in seizure frequency. Over the 3-month evaluation period the treatment group maintained or increased this reduction, however, at the end of the evaluation period seizure frequency in the sham group had approached the pre-implant frequency. Interestingly the responder rate was similar in both groups (defined as those patients with a $\geq 50\%$ reduction in seizures) with 29 and 27 per cent of patients in the treatment and sham groups, respectively, being considered responders. During the evaluation period two patients from the treatment group, compared to none in the sham group, were seizure free. By the third month of the

evaluation period, the treatment group had 27 per cent fewer days with seizures compared to 16 per cent in the sham group.

Table 3 Mean per cent change in seizure frequency during the evaluation period¹²

	Treatment (n=97) Mean % change [95% CI]	Sham (n=94) Mean % change [95% CI]	p value
Month 1 (3-months post-op)	-34.2% [-44.1, -22.6]	-25.2% [-37.1, -11.1]	0.008
Month 2 (4-months post-op)	-38.1% [-47.3, -27.3]	-17.2% [-30.5, -1.3]	0.016
Month 3 (5-months post-op)	-41.5% [-52.0, -28.7]	-9.4% [-29.5, 16.4]	0.279
Entire evaluation period	-37.9% [-46.7, -27.7]	-17.3% [-29.9, -2.3]	0.012

Once patients entered the open label period, when all patients received neuro-stimulation, the patients in the sham group had a statistically significant reduction in mean seizure frequency compared to the pre-implant period ($p=0.04$) (Figure 3). When patients were considered as a whole during this open label period, seizure reduction was sustained and improved over time. The responder rate at 1 year post-implant was 43 per cent ($n=177$) and for the 102 patients who had reached 2-year post-implant follow-up, the responder rate was 46 per cent. At this cut-off point, 13 patients reported being seizure free over the last 3-month data collection period. At the end of the evaluation period, quality of life in epilepsy scores improved in both the treatment and sham groups ($p=0.04$ and $p=0.032$, respectively). These improvements continued for all patients at the end of one ($p<0.001$) and two years ($p=0.016$) in the open label period.¹²

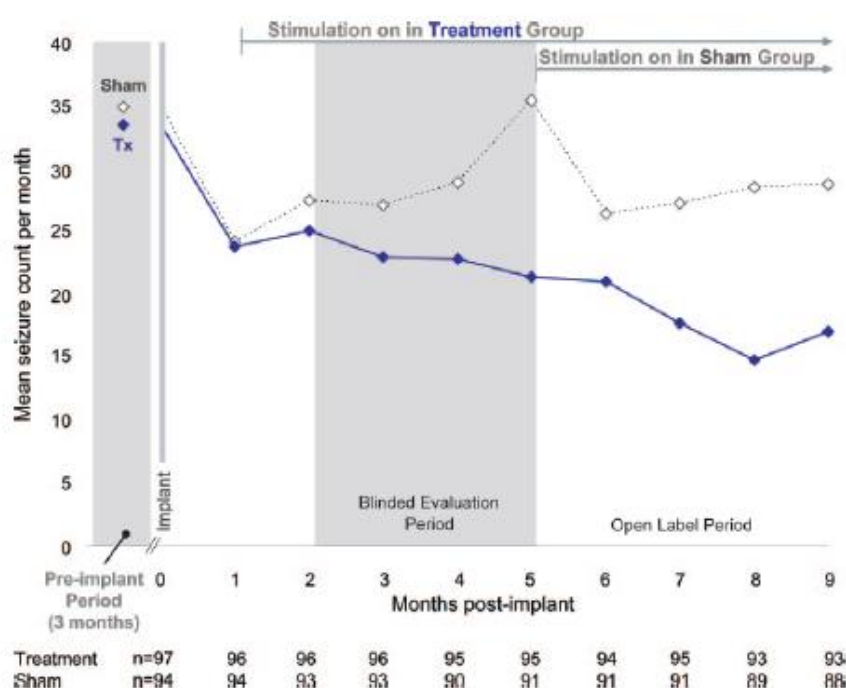


Figure 3 The mean number of disabling seizures by month (observed data)¹²

These patients have continued to be followed up. In addition, NeuroPace intends to begin a post-approval study in the United States, as agreed upon with the FDA, early to mid-2014 (personal communication NeuroPace). Another *treatment* option is the VNS Therapy™ System, which provides repeated electrical stimulation to the left vagus nerve with the aim of *preventing* seizures. The device, which is similar to a pacemaker in appearance, is implanted in the upper chest and electrodes are attached to the vagus nerve in the neck. VNS Therapy™ was assessed by [HealthPACT in 2007](#) and was the subject of an [MSAC application in 2008](#). Public funding was not approved for the implantation of this device on the grounds that there was insufficient evidence of effectiveness and net benefit of VNS therapy for patients with medically refractory epilepsy. A [proposal](#) to reconsider the VNS Therapy™ System is currently being considered by MSAC.

Ongoing research

The Australian research team have no human trials currently planned, but are developing a less invasive device that will hopefully allow prediction at the same level as the 2013 study. The researchers are currently optimising certain technical aspects of the device. The group has some limited animal data and hope to perform a study in larger animals in 2014 (personal communication).

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